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09/654,373	09/01/2000	Sean C Semple	INEX.P-007	5857

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EXAMINER
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NAFF, DAVID M

ART UNIT	PAPER NUMBER
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1651  
DATE MAILED: 07/28/2003 (P)

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.	09/654373	Applicant(s)	Sample et al
Examiner	Waff	Group Art Unit	1051

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

### Status

Responsive to communication(s) filed on 5/27/03

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

### Disposition of Claims

Claim(s) 1-9 is/are pending in the application.

Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

Claim(s) \_\_\_\_\_ is/are allowed.

Claim(s) 1-9 is/are rejected.

Claim(s) \_\_\_\_\_ is/are objected to.

Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

### Application Papers

- See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- The proposed drawing correction, filed on \_\_\_\_\_ is  approved  disapproved.
- The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- The specification is objected to by the Examiner.
- The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. § 119 (a)-(d)

- Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
  - All
  - Some\*
  - None of the CERTIFIED copies of the priority documents have been received.
- received in Application No. (Series Code/Serial Number) \_\_\_\_\_.
- received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

### Attachment(s)

<input type="checkbox"/> Information Disclosure Statement(s), PTO-1449, Paper No(s). _____	<input type="checkbox"/> Interview Summary, PTO-413
<input type="checkbox"/> Notice of Reference(s) Cited, PTO-892	<input type="checkbox"/> Notice of Informal Patent Application, PTO-152
<input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review, PTO-948	<input type="checkbox"/> Other _____

## Office Action Summary

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) 5 has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/27/03 has been entered.

The amendment of 4/28/03 after final rejection has been entered. The amendment amended the specification and claim 1, and canceled claims 10 10-22.

Claims examined on the merits are 1-9 which are all claims in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

15 **Specification**

The amendment filed 4/28/03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention.

20 The new matter results from changing the paragraph at page 10, lines 21-24 by adding and deleting material. The added material recites "The ionizable lipid is selected such that small multilamellar vesicles are substantially free of external non-encapsulated oligodeoxynucleotides at physiological pH. The term "physiological pH" refers to pH levels 25 conventionally encountered in serum or blood. In general, this will be

in the range of pH 7.2 to 7.5. Ionizable lipids have a pKa such that they are substantially neutral at this pH, i.e., a pKa of about 4 to 7 in the case of an amino lipid".

The deleted material recites ", and DOGS".

5       Applicants assert that the added description is supported throughout the application, and in particular in the examples. However, the added material is not recited in the specification, and adequate support for the disclosure is not readily apparent in the description and examples. Apparently, the added subject matter is derived or extrapolated from the  
10 specification, and it is unclear how the extrapolation was carried out.

Applicants cite parent application 09/078,954 (page 12) for the added definition of physiological pH. However, there is inadequate support that preferred amino lipids being substantially neutral at physiological pH as disclosed in the parent application were also  
15 preferred in this application since this application is a CIP of the parent application and discloses an invention different than in the parent application. Additionally, the parent application does not use the term ionizable lipid, but instead refers to protonable or deprotonatable lipids as having the pKa to be substantially neutral.

20       The deletion of DOGS changes the disclosure of the invention from that originally filed. There is inadequate evidence to establish that reciting "DOGS" was an error and that DOGS is not an ionizable lipid that will work in the invention.

Applicants refer to an article by Barthel et al as disclosing at  
25 page 555 that 2 mM DOGS (lipospermine) contains 6 nM ammonium cationic

charges at neutral pH. However, the present specification as originally filed contained no limitation as to a maximum amount of cationic charges that can be present at neutral pH for the ionizable lipids used. While the parent application discloses preferred amino lipids as being 5 substantially neutral at a pKa of about 4 to 7, it is not clear that this was also preferred in the present CIP application which discloses a different invention than in the parent application. Even if the preferred amino lipids in the parent application are also preferred in the present application, there is inadequate support that a pKa range of 10 4 to 7 excludes charges as disclosed by Barthel et al. Furthermore, the parent application recites "substantially" neutral and "substantially" is a broad term that can encompass a considerable amount of charges at neutral pH, and even the amount of charges disclosed by Barthel et al. Applicants have made no comparison of the charges present when expressed 15 as disclosed by Barthel et al when the amino lipid is DODMA and DODAP.

Applicant is required to cancel the new matter in the reply to this Office Action.

**Claim Rejections - 35 USC § 112**

The following is a quotation of the first paragraph of 35 U.S.C.

20 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set 25 forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

5 The original specification fails to support the added limitation to claim 1 reciting "wherein the ionizable lipid is selected such that the small multilamellar vesicles are substantially neutral at physiological pH". The recitation is not recited in the original specification, and 10 adequate support is not found for the limitation. While the parent application discloses preferring amino lipids that are substantially neutral at physiological pH, there is inadequate support that this was also preferred in the present CIP application which discloses a different invention. Moreover, even if using an amino lipid that is substantially 15 neutral at physiological pH as disclosed in the parent application supports using this amino lipid in the invention of the present application, this does not support that the small multilamellar vesicles resulting from using the amino lipid were also intended to be substantially neutral at physiological pH.

20

***Claim Rejections - 35 USC § 103***

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wheeler et al (WO 96/40964) for reasons set forth in the previous office action of 1/28/03 and for reasons herein.

25 The claims are drawn to oligodeoxynucleotide-containing lipid vesicles in an aqueous carrier wherein a portion of the vesicles are

multilamellar vesicles containing 20-30% ionizable amino lipid, a steric barrier lipid and neutral or sterols, and oligodeoxynucleotides in the lumen or interlamellar spaces of the multilamellar vesicles, wherein the ionizable lipid is selected such that the small multilamellar vesicles  
5 are substantially neutral at physiological pH.

Wheeler et al disclose encapsulating a therapeutic agent such as antisense oligonucleotides or ribozymes (page 17, lines 14-15) in a lipid bilayer (page 23, lines 3-15, and page 26, line 23) prepared from cationic and non-cationic lipids (page 4, lines 2-7, and page 26, line 10 17) to provide lipid particles of about 50-150 nm in size containing encapsulated nucleic acid. The cationic lipid is an amino lipid (page 15, line 16) and the non-cationic lipid may be polyethylene glycol conjugated to ceramides such as PEG-CerC14 (page 25, lines 17-20, and Table 1 (page 53) and Table 2 (page 54)). As shown in the tables, lipid 15 mixtures containing an amino lipid, a mixture of neutral lipids and a PEG-ceramide are used to encapsulate nucleic acids. The lipid encapsulated nucleic acid can be used to treat a patient by gene therapy to suppress gene expression (paragraph bridging pages 42 and 43).

The lipid particles containing encapsulated nucleic acids of Wheeler 20 et al can be multilamellar, have the same composition and inherently have oligodeoxynucleotides as presently claimed. It would have been obvious to put the particles in an aqueous carrier for therapeutic use.

The added recitation to claim 1 requiring the ionizable lipid to result in substantially neutral vesicles at physiological pH does not 25 distinguish over Wheeler et al since DOGS used by Wheeler et al is an

ionizable lipid and would result in such substantially neutral vesicles. The term "substantially" is broad and would permit charges that can be present when using DOGS, and the present specification originally disclosed using DOGS as an amino lipid.

5

***Response to Arguments***

Applicants urge that the disclosure in the present specification of using DOGS is an error. However, for reasons set forth above, the disclosure of DOGS being an error is not adequately supported by evidence. While DOGS may result in charges at physiological pH, the 10 original specification nowhere discloses a limit on charges that can be present at a particular pH. The disclosure from the parent application of being substantially neutral at physiological pH does not exclude DOGS since "substantially" before neutral is sufficiently broad to encompass charges that may be present at physiological pH when using DOGS.

15

***Double Patenting***

Claims 1-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-72 of U.S. Patent No. 6,287,591 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the 20 presently claimed composition would have been obvious from the claims of the patent drawn to nucleic acid-containing vesicles.

***Response to Arguments***

Applicants indicated in a response of 10/29/02 that a terminal disclaimer will be filed when allowable claims are determined.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is (703) 308-0520. The examiner can normally be reached on Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn, can be reached at telephone number (703) 308-4743.

The fax phone number is (703) 872-9306 before final rejection or (703) 872-9307 after final rejection.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



DAVID M. NAFF  
PRIMARY EXAMINER  
ART UNIT 1651

20 DMN  
7/25/03